Effect of Selenium supplementation in modulating Sarcopenia outcomes through Gut dysbiosis in Ulcerative Colitis patients

SHORT SYNOPSIS

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Certificate

I hereby declare that the short synopsis Title **"Effect of Selenium supplementation in modulating Sarcopenia outcomes through Gut dysbiosis in Ulcerative Colitis patients"** being submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Biochemistry under School of ALLIED HEALTH SCIENCES of Manav Rachna International Institute of Research & Studies, Faridabad during the academic year 2023-2024. It is a bona fide record of original work carried out under the supervision of Dr. Gurseen Rakhra and has not been submitted in full or part to any other university or institute for degree or diploma. Further, it is certified that short synopsis is plagiarism free and proof has been submitted.

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ABSTRACT

Inflammatory Bowel disease (IBD) has become a global health issue on national and international platforms. IBD shows two main types as per its location; one is Ulcerative Colitis (UC) and the second is Crohn's disease (CD). UC has three stages mild, moderate, and severe. Patients suffering from UC have a great risk of malnutrition and micronutrient deficiency such as iron, zinc, copper, Manganese, and selenium. Selenium (Se) deficiency is a common micronutrient deficiency in UC patients. The deficiency arises due to the competitive demand of the human body and microbiota in UC patients for Se. Se has antioxidant properties that help reduce the severity in UC patients. Gut dysbiosis is one of the factors of UC that appears due to a disbalance in beneficial and harmful bacteria produced in the gut. Another hallmark of UC is sarcopenia which develops due to chronic inflammation. In addition, sarcopenia is caused due to gut dysbiosis and micronutrient deficiency. Se as an oral supplement can target gut dysbiosis, sarcopenia, and UC symptoms. In this study, Se as an oral supplement will be given to patients in the form of Selenomethionine to improve the symptoms and severity of sarcopenia by targeting gut dysbiosis in UC patients.

Keywords: Ulcerative Colitis (UC), Sarcopenia, Selenium (Se) and gut dysbiosis

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1. Introduction:

Inflammatory Bowel Disease (IBD) has evolved into a manageable chronic condition from a fatal disease and has two main types; one is UC and the other is CD (McDowell *et al*, 2024). CD was discovered in 1623 by Wilhelm Fabry whereas UC was described by Samuel Wilks in 1859 (Baumgart & Carding, 2007) (Mulder et al., 2014). IBD is a global menace that has increasing incidence globally (Zhang & Li, 2014). Western countries have shown high prevalence leading up to 2 million patients. New studies at the epidemiological level revealed that people in developing countries like Asia, Africa, South America, and Eastern Europe are becoming more prone to this disease (Ramos & Papadakis, 2019). It is characterized by chronic remission and relapse inflammation of the gastrointestinal tract (Amerikanou et al., 2022). The gastrointestinal tissue is impacted by IBD, a chronic inflammatory disease that is strongly linked to nutritional deficiencies and metabolic abnormalities that raise the risk of sarcopenia (Fatani, H. *et al*, 2023). A gradual loss of muscle mass causes sarcopenia, which is typically a concern in the elderly. According to the updated European agreement, the presence of low muscle strength in addition to low muscle strength and low muscle mass confirms sarcopenia's identification, whereas low muscle strength existence indicates likely sarcopenia. Low physical performance in the presence of sarcopenia is a sign of severe sarcopenia. IBD has also been linked to sarcopenia. Malnutrition, malabsorption, Chronic inflammation and gut dysbiosis are some of the mechanisms causing sarcopenia in people with IBD. The sarcopenia confirmation in IBD and its effect on surgical outcomes have been documented in some recent studies that have modified the mainstream definition of sarcopenia (considering both muscle mass and muscular strength). There hasn't been any research done on the connection between sarcopenia and UC in adults (Neelam, P. *et al*, 2024).

One of the most prevalent conditions that results in malabsorption is IBD. Sarcopenia is closely linked to malabsorption syndrome, a disorder that arises when nutrient absorption from food is decreased in the small intestine for a variety of causes. Inflammatory mediators like TNFα and IL-6 are released when the gut becomes inflamed, increasing intestinal permeability and producing both local and systemic inflammatory consequences. It is believed that sarcopenia in IBD is largely caused by chronic inflammation. Pro-inflammatory cytokines like interferon IL-1, IL-6, IFN-γ, and particularly tumor necrosis factor-Alpha (TNF) α are elevated systemically in IBD patients. Reduced muscle protein synthesis and protein catabolism are linked to inflammatory cytokines. Although it is well recognized that the adipokines released by adipocytes are crucial for maintaining the balance of energy metabolism, they also have a role in immune system regulation and muscle protein homeostasis. Inducing inflammatory responses through the activation of transcription factors like NF-κB and signal transducer and activator of transcription 3 (STAT3) is recognized to be the mechanism by which adipocytes manufacture pro-inflammatory cytokines such as free fatty acids, IL-6, and TNF-α. Adipose tissue inflammation may contribute to the onset of sarcopenia and is linked to the worsening of IBD (Nishikawa, H *et al*, 2021).

Skeletal muscle fibers detect an excess of reactive oxygen species (ROS) and oxidative stress (OS) by the expression of cytokine-associated receptors and the (TLR) toll-like receptor-2 and TLR-4, which potentially bind to LPS. Oxygen intake reduces mitochondrial respiration and ATP production because mitochondria are the cellular organelle most susceptible to ROS. This mechanism causes "mitophagy." Increased systemic inflammation has been linked to mitochondrial dysfunction, which affects muscle protein synthesis and compromises both mitochondrial and muscular function and are therefore likely to play a role in the evolution of sarcopenia. The function of epithelial mitochondrial stress in the pathophysiology of UC is still unclear, even though dysfunction of mitochondria has already been established in the intestinal epithelium in individuals suffering from IBD. The

microbiota and mitochondrial function are closely related. However, compared to healthy people, IBD patients usually have lower levels of bacteria in their mucosa and feces that ferment fibers and create SCFAs. The gut microbiota's low proportion of SCFA makers has been linked to elevated subclinical chronic inflammation, which strengthens the anabolic resistance of skeletal muscle. Skeletal muscle tissue and the gastrointestinal tract interact through a complex network that is regulated by the Gut microbiota (GM). The questionable "gut dysbiosis," which is an indecent immunological effect of a convoluted microbial community to intestinal inflammation, is caused by changes in this ecosystem in IBD patients, including changes in biodiversity, microbial composition, and microbial roles. IBD patients have been found to have a higher proportion of mucolytic bacteria, which control the breakdown of barrier in the mucosa and consequently lead to a greater attack of pathogens into the tissues of the intestine and a lower proportion of Firmicutes and Bacteroides, which compromise the integrity of the intestinal barrier. This illness, known as "leaky gut syndrome," is a contributing factor to the development of a pro-inflammatory state that results in sarcopenia in both older people and those with IBD (Nardone, O. M. *et al*, 2021).

An important trace element in humans, selenium (Se) has come to light as being involved in the regulation of inflammatory signaling pathways that are implicated in the etiology of UC The main way that Se contributes to physiological processes is via being incorporated into selenoproteins, where it is found as the amino acid selenocysteine. These selenoproteins are essential for immune system regulation, oxidative damage prevention, and inflammatory response inhibition. Selenium supplementation leads to a decrease in inflammation of the intestine by the activation of the Nrf2 and NF-κB signaling pathways. Se has also been shown to suppress T-cell differentiation and oxidative stress, which helps the gut barrier heal and regenerate. These results highlight selenium's complex involvement in gut health and its potential benefits for both preventing and treating intestinal disorders, especially IBD (Liu, S. *et al*, 2024). One of the necessary trace elements is selenium, and it has been noted that individuals who are deficient in this element experience skeletal muscle illness, which is characterized by fatigue, proximal limb weakness, muscle discomfort, and increased serum creatine kinase. Mice experiments demonstrate that selenium supplementation improves skeletal muscle function by increasing calcium release from the sarcoplasmic reticulum, and that elevated selenoprotein N expression in muscle improves resistance to oxidative stress (Liu, S. *et al*, 2023). Glutathione peroxidase activity was markedly reduced by selenium depletion, which also caused intestinal flora disruption, most notably a reduction in Lactobacillus reuteri (Wang, G.*et al*, 2024). Furthermore, it has been proposed that Se influences the gut microbiota. Few studies have documented links between altered gut microbiota and gut metabolites brought on by Se supplementation, even though Se and other dietary minerals have been shown to influence gut microbiota (Callejón-Leblic, *et al*, 2021).
The current study is designed to focus on Selenium supplementation in UC patients. We would be linking the role of selenium in improving sarcopenia in UC patients through the modulation of gut dysbiosis as its impact is limited in the available literature. As of now, very few studies explored the connection or link between Gut dysbiosis, and sarcopenia in IBD patients at national (Indian population) and International platforms. This study would help to establish the role of Se in improving sarcopenia in IBD (UC) patients by targeting gut dysbiosis.

2. Literature Review and Research Gap

Sarcopenia in Ulcerative Colitis patients

1. A cross-sectional evaluation of sarcopenia in UC patients was carried out. The full Mayo score was used to rate the disease activity. A dual-energy X-ray absorptiometry scan was used to measure muscle mass, a 4-meter walk test was used to evaluate physical performance, and a Jamar hand dynamometer was used to measure hand grip strength. Out of 114 patients (62 male), 32 (28%) were in remission, 46 (40.4%) had mild-moderate activity, and 36 (31.6%) had confirmed severe UC. Forty-three patients (37.7%) had probable sarcopenia, 25 (21.9%) had sarcopenia, and 14 (12.2%) had official severe sarcopenia. The preponderance of sarcopenia was higher in active disease (2 in remission, 6 inactive, and 17 in severe). Out of 114, 14 had severe sarcopenia, 13 had severe UC and 1 had moderate UC (Neelam, P. B. *et al,2024).*

2. Retrospective inclusion was made of 254 ASUC patients who had CT scans performed at admission. Sarcopenia was identified in patients whose skeletal muscle index (SMI) was below the lowest percentile for that sex . The SMI was measured using CT scans at L3. A BMI of less than 18.5 kg/m2 was considered clinical malnutrition.
Malnutrition was 25.2% and sarcopenia was 50.0% prevalent in ASUC. Of individuals with sarcopenia, 51.2% had a normal BMI, 11.8% were overweight, 0.8% were obese, and 36.2% were malnourished (Ge, X. *et al,* 2022).

3. Four tertiary referral hospitals in China participated in this multicenter, prospective, observational investigation. Data on demographics recent weight change, disease background, handgrip strength (HGS), and BC parameters using Bioelectrical impedance analysis (BIA) were gathered from consecutive IBD inpatients. Stepwise screening (Nutritional Risk Screening 2002) and diagnosis were used to conduct nutritional assessments. The Inflammatory Bowel Disease Questionnaire was used to measure quality of life. This study recruited 238 IBD patients, 68.5% of whom were male individuals, with a mean age of 38.5 ± 14.0 years, a mean BMI of 19.8 kg/m2, and 177 CD and 61 UC patients. In contrast to MHC (n = 122), IBD patients exhibited a marked decline in BC and physical function, as evidenced by aggregation of fat and muscle depletion (appendicular skeletal muscle mass index [ASMI] (Zhang, Y. *et al, 2023).*

4.There were 60 controls, 105 Crohn's disease (CD) patients, and 99 UC patients in this study. Computed tomography (CT) of the abdominal region was used to assess the skeletal muscle area (SMA) of the third lumbar vertebrae subcutaneous fat area (SFA) and visceral fat area (VFA). It was established how medical treatment and surgery affected the body composition of UC patients. Sarcopenia was less common in CD patients (59.0%) but more common in UC patients (27.3%) compared to controls (8.3%). SMA and skeletal muscle index (SMI) were substantially decreased in UC patients with high (≥6) than low (<6) Mayo scores, although SFA and VFA were equal. The preponderance of sarcopenia was significantly higher (Zhang, T. *et al,* 2017.)

Gut Dysbiosis in Sarcopenia patients

1. Nikkhah *et al,* Conducted a systematic study until July 2021, a methodical search on the PubMed, Web of Science, and Scopus databases using pertinent keywords. They chose original English-language animal studies and human observational research that was relevant to our research subjects.

The main change in sarcopenia caused by liver cirrhosis and age-related sarcopenia, was reduction in bacterial species that produce short-chain fatty acids (SCFAs). Age-related sarcopenia was substantially reduced in the Lachnospiraceae family, which includes Lachnospira, Fusicatenibacter, Roseburia, and Lachnoclostridium (Nikkhah, A. *et al, 2023).*

2.The baseline features of UC and CD patients were compared to those of healthy controls. According to radiological, histological, and clinical criteria, every patient had a confirmed diagnosis. Se supplementation was not given to any patients or healthy subjects. A single gastroenterologist performed all colonoscopies and scored the endoscopic scores. The selenium levels were hidden from the gastroenterologist. The sum of the points for every parameter is the overall CAI score. In general mild to moderate and severe disease activity and remission or very mild disease are indicated by CAI scores of 0–4, 5–10, 11–15, and 16–21, respectively. The Rachmilewitz Index, sometimes referred to as the CAI for ulcerative colitis, gauges the severity of the condition using particular clinical criteria. The sum of the scores for each criterion determines the overall CAI score. The scoring system includes Zero points for 0–1 stool and three points for more than 6 stools every day. Scores for blood in feces range from 0 (no blood) to 3 (highest blood). From Zero points for feeling extremely good to four points for feeling awful.
According to Lichtiger et al., 21 UC patients showed high disease activity and were deemed to be in the active phase if their Clinical Activity Index was higher than 5. Furthermore, there was minimal disease activity in 25 UC patients. We additionally evaluated variations in selenium levels based on the CAI scale's disease severity score. According to statistical analysis, the severity of the condition was associated with a statistically significant drop in selenium concentrations (Chalcarz, M. *et al,2024).*

Role of Selenium in UC patients

1.56 UC patients (29 in remission phases and 29 in flare-up) and 29 healthy volunteers participated in a prospective case-control research at Ahvaz Imam Hospital in 2019. Atomic absorption spectroscopy was used to measure serum Se concentrations in blood samples taken from both sick and healthy people. The control group's serum Se concentration was 109.91 g/mL, the flare-up groups' was 98.40 g/mL, and the UC remission group's was 112.40 g/mL. Serum Se concentrations were considerably lower in UC patients experiencing flare-up disease than in controls (P=0.0001) and patients in remission (P=0.0001). Serum Se concentrations did not significantly differ between remission patients and controls (P=0.338). Serum Se concentrations are lower in UC flare-up patients than in UC patients in remission and control groups. To ascertain whether nutritional supplements may enhance the clinical course of UC, more research is required (Alavinejad, P. *et al,* 2024).

2.From January 1980 to December 2023, a thorough search of online databases was carried out with an emphasis on research on selenium levels in inflammatory bowel disease patients. Using a random-effects model, the association between IBD and Se levels in patients and controls was examined.
Based on the inclusion criteria, 20 studies with 1792 IBD individuals and 1648 controls were chosen from the 1853 references that were searched. According to the meta-analysis, selenium levels are considerably lower in individuals with inflammatory bowel disease than in the control group. According to the analysis, selenium levels are significantly lower in patients with inflammatory bowel disease, particularly those with Crohn's disease, than in controls. This suggests that selenium supplementation could be a useful addition to the treatment plan for inflammatory bowel disease, especially in patients who have been diagnosed with selenium insufficiency (Liu *et al, 2024).*

3.1999–2006 and 2011–2018 data of 19,696 participants from the National Health and Nutrition Examination Survey (NHANES) were examined in this cross-sectional study. As a marker for sarcopenia, DXA was utilized for the measurements of appendicular muscle mass and corrected for BMI. The 24-hour dietary recall approach was used to assess dietary selenium consumption, and the study took into consideration the intricate sampling procedure and included food sample weights in the analysis. It was discovered that 8.46% of the 19,696 participants had sarcopenia. Sarcopenia and dietary selenium intake were found to be negatively correlated (non-linear: $p = 0.285$). Additionally, after controlling for blood selenium levels, sensitivity tests showed a strong correlation between selenium intake and the occurrence of sarcopenia (Li *et al,2024).*

4.100 individuals with active mild-to-moderate UC were included in a multicenter, double-blind, RCT. For ten weeks, the patients were randomized to receive either a placebo capsule ($n = 50$) or an oral selenomethionine capsule (200 mcg/day). The Simple Clinical Colitis Activity Index (SCCAI) was used to determine the primary outcome, which was disease activity. Secondary outcomes were assessed after the trial. The Se group's mean SCCAI score decreased after 10 weeks ($P<0.001$). After the intervention, nineteen patients (38%) in the Se group and three patients (6%) in the placebo group showed clinical improvement (a decrease of 3…score from baseline score). Patients in the Se group ($P = 0.014$) had clinical remission, which is defined as SCCAI < 2. By the end of the trial, both the serum levels for Se and the quality of life Se group had shown improvement ($P < 0/001$) (Khazdouz, M. *et al*, 2023)

Research Gap:

The effect of Se supplementation in modulating sarcopenia in UC patients through gut dysbiosis is not known. However it is known that Se deficiency is linked to UC. Thereby, targeting Se to improve the symptoms and severity in UC patients.

3. Description of Broad area and Problem statement

Selenium (Se) is a vital micronutrient that plays important functions in the immune system, antioxidant system, cancer prevention, and hormone regulation. Se's therapeutic roles have been linked mostly to its presence in the form of selenoproteins. Specifically, Selenocysteine is accountable for influencing inflammatory path. Se subjunction showed protective functioning against tissue damage in experiments in UC patients by affecting the expression of genes involved in the regulation of mitochondrial cell death which can help in improving the sarcopenia associated with gut dysbiosis in the UC patients. Se supplementation may function as a preventive factor for inflammation through the regulation of certain gene expressions involved in immune upshot insufficiency is a common finding in IBD patients but has gotten little attention. This micronutrient has a long history of anti-inflammatory activity, which has been highlighted in autoimmune, allergy, and chronic inflammatory illnesses. Initially, the anti-inflammatory benefits of selenium were attributed solely to the antioxidant effects of selenoproteins.

The available current literature do not show any study in which Se supplementation is given to the patients having gut dysbiosis, sarcopenia in UC patients.

4. Research Objectives:

1: To assess the prevalence of Sarcopenia, gut dysbiosis and Se deficiency among UC patients

2: To determine the effect of Se supplementation on Gut dysbiosis in UC patients

3: To examine the effect of Se supplementation on Sarcopenia outcomes in UC patients

5. Research Methodology:

Inclusion criteria: Patients (Male and female) with confirmed gut dysbiosis (Dysbiosis-Risk questionanaire) and sarcopenia (confirmed by Bioelectrical Impedence Analysis, Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F), SARC-F plus calf circumference (SARC-Calf) and anthropometric measurements) and selenium deficiency (< 90 microgram/L) among Ulcerative colitis

Exclusion criteria: Pregnant females and co-morbidities (heart failure, diabetes mellitus, kidney disease and COPD) and patients on other diseases medications

METHODOLOGY

Patients with UC would be assessed through UCEIS score and truelove and witts criteria

Moderate to severe patients

- Screening of UC patients for Sarcopenia according to AWGS parameters (Appendicular muscle mass and strength by BIA, anthropometric measurements, SARC-Calf) and SARC-F questionnaire
- Assessment of Gut dysbiosis by Dys-R questionnaire
- Selenium deficiency estimation < 90 μg/L by ICP-MS

Inclusion criteria: Patients with Sarcopenia, gut dysbiosis and Se < 90 μg/L

Gut dysbiosis and sarcopenia measure

Single blind method

Control (n=30)

Experimental (n=30)

Placebo

Selenomethionine (200μg/day) for 3 months

Assessment of Changes in Gut dysbiosis and Sacropenia symptoms and severity in UC patients

Steps in Methodology

1.Ulcerative Colitis patients (moderate to severe) would be assessed for severity by UCEIS (Ulcerative Colitis Endoscopic Index of Severity) and truelove and witts criteria.
2.UC patients would be assessed for Sarcopenia as per AWGS parameters like ASM by BIA and muscle strength, Anthropometric measurements, SARC-Calf and SARC-F questionnaire.
3. The next step will be to assess gut dysbiosis with a Dysbiosis risk (Dys-R) questionnaire.
4. Estimation of Selenium deficiency (< 90 microgram/L) by ICP-MS
5. Then, the single-blind method will be followed and patients will be divided into control and experimental groups with n=30 for each.
6. Now, Se supplementation will be given of Selenomethionine for 3 months with a dose 200 μg/day in the experimental and a placebo to the control group.
7. Assessment would be repeated again after 3 months of supplementation.
8. The assessment of sarcopenia and gut dysbiosis symptoms after Se supplementation would be checked for any change in symptoms and severity.

6. Expected Outcomes:

The study aims to establish the role of Selenium supplementation in improving sarcopenia outcomes by modulating the gut dysbiosis in UC patients and ultimately leading to improved quality of Life (QoL).

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Research Ethics Committee
MRIIRS, FARIDABAD
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Email-dean.research@mriu.edu.in

24th January, 2025

Dr.Gurseen Rakhra
Supervisior
Assistant Professor
Department of Nutrition & Dietetics,
School of Allied Health Sciences
MRIIRS,
Faridabad- 121001

Dear Dr. Gurseen Rakhra
The MRIIRS Ethics Committee has reviewed your request, for the ethical approval for the research project outlined below.

"Effect of Selenium supplementation in modulating Sarcopenia outcomes through Gut dysbiosis in Ulcerative Colitis patients."

Mr. Rajan Malhotra
Research Scholar
MRIIRS
Registration number: 22-23/Ph.D/W/001

The case is discussed in the meeting of Ethical Committee, MRIIRS held on 26/12/2024 vide Online Mode at 1.30 pm.

https://meet.google.com/afw-bphq-hwz
Further, on examining the research work undertaken vide video presentation mode given by the Research Scholar, as indicated above, it was resolved that ethical approval may be granted as the research scholar will obtain consent of Ulcerative Colitis patients with gut dysbiosis and sarcopenia enrolled in the study as participants. The consent letter format / form both English and Hindi has been submitted. The form and certificate can be used for carrying out a research study at Ram Manohar Lohia Hospital, Delhi.

The required documents as asked in the meeting have been submitted today i.e. 24.01.2025 by Dr. Gurseen Rakhra , Assistant Professor, Supervisor, School of Allied Health Sciences, MRIIRS

Approval No:	EC/2024-25/057
Approval Date:	24.01.2025
Expiry Date:	01/02/2027
Ethics Committee Decision	Approved

The standard conditions of this approval are:

a) Conduct the project strictly in accordance with the proposal submitted and granted ethics approval. Including any amendments made to the proposal required by the MRIIRS Ethics Committee.

b) Report (email: dean.research@mriu.edu.in) immediately of any complaints or other issues in relation to the research project which may warrant review of the ethical approval of the project.

c) provide a 'progress report' for every year of approval.
d) provide a 'final report' when the project is complete.
e) advise in writing if the project has been discontinued

Please note that failure to comply with the conditions of approval and the **"INDIAN COUNCIL OF MEDICAL RESEARCH. 2017.** NATIONAL ETHICAL GUIDELINES. **FOR BIOMEDICAL AND HEALTH RESEARCH INVOLVING HUMAN"** may result in withdrawal of approval for the research project.

24.1.25

Dr Sarita Sachdeva
ED & Dean Research
MRIIRS

Dean Research
Manav Rachna International Institute
of Research & Studies
Sector 43, Aravali Hills, Surajkund Road,
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SIMILARITY VERIFICATION CERTIFICATE

Title: Effect of Selenium Supplementation in modulating Sarcopenia Outcomes through Gut Dysbiosis in Ulcerative Colitis patient

Researcher: Rajan Registration Number: 22-23/P.L.D/W/001

Supervisor: Dr. Gurseen Rekhea Department: N.R.D

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Research Scholar

Research Supervisor

Rajan

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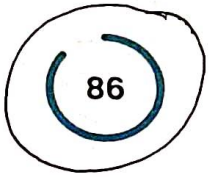

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